REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 23, 24, 28-33, 35, 40, 42-46, 48-52 and 54-60 are in this case. Claims 23, 24, 28-33, 35, 40, 42-46, 48-52 and 54-60 have been rejected. Claims 32, 45 and 51 have now been amended. Claims 57 and 58 have now been cancelled. New claims 61-83 have now been added.

35 U.S.C. §112, Second Paragraph, Rejections

Claims 57-58 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner states that Claims 57 and 58 are indefinite because they depend from cancelled claim 34.

Claims 57 and 58 have now been cancelled, thereby rendering moot Examiner's rejection thereof.

35 U.S.C. §103, Rejections

The Examiner has rejected claims 23, 24, 28-33, 35, 40, 42-46, 48-52 and 54-60 under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent Application No. 2004/0266717 (Donahue et al.) and Koh et al. (1995).

The Examiner states that Donahue et al. use a polynucleotide capable of modulating an electrical property in a standard cardiac electrophysiological assay and expressing the polynucleotide (e.g., polynucleotides which encode a K cannel subunit, a Na channel subunit and a Ca channel subunit) in the mammal to prevent or treat heart disease.

The Examiner states that Koh et al. (1995) disclose successful engraftment of fetal canine cardiomyocytes into the hearts of adult CXMD (canine X-linked muscular dystrophy) dogs, wherein Connexin43 immunoreactivity was shown at junctional complexes between the donor and host cells.

The Examiner concludes that given Donahue et al. disclose ion channel gene delivery for the treatment of cardiac arrhythmias and Koh et al. provides evidence that methods for engrafting cardiomyocytes are known in the art and that gap junctions form upon engraftment, the skilled artisan would have been motivated to transfect cardiomyocytes ex-vivo using the

polynucleotides taught by Donahue et al. and then implant the cardiomyocytes into the mammalian heart.

The present invention relates to the transplantation of isolated cells which express exogenous ion channels to modify the electrophysiological function of any excitable tissue region transplanted therewith, by tissue remodeling.

The present inventors were the first to show that introduction of cells which express exogenous ion channels into an excitable tissue can be used to control the electrophysiological function of excitable tissues, to thereby treat various disorders associated with such tissues (see Example 5 of the Examples section of the instant application as well as the Appendix section, which was attached to the response filed March 3, 2003).

In sharp contrast to the present invention, Donahue et al, merely teach the use of in vivo gene transfer of a number of therapeutic genes, including those encoding ion channels, for the treatment of cardiac disorders alone. Interestingly, although cell therapy procedures were known in the art at the time of filing the application by Donahue et al. and were even considered as safer and more predictable than the in vivo gene therapy approach, Donahue et al. did not describe nor suggest using same for the treatment of cardiac disorders. In fact the only mentioning by Donahue et al. of ex-vivo gene therapy procedures, is in relation to the selection of the transferred polynucleotide, a selection which is based on a "standard electrophysiological assay" (e.g., see paragraph 0081). This strongly supports that although Donahue and co-workers were aware to the possibility of ex-vivo gene therapy, they did not consider using same for the treatment of cardiac diseases.

In fact, Donahue et al. considers cell therapy merely *"as indirect means of delivering new genes and proteins to the heart"* as is evidenced from a later review attached herewith [Tomaselli and Donahue 2003 J. of Cardiovascular Electrophysiology 14:547-550]. In this way cells are used as a vector for providing the ion channel sequences to cells of the target tissue via cell fusion.

With respect to Koh et al. Applicant wishes to point out that although Koh et al. disclose the transplantation of cardiomyocytes into dog's heart for the purpose of increasing the number of functional cardiomyocytes in a diseased heart (i.e., increasing cell mass), as opposed to modifying the physiological properties of the heart, Koh et al. do not describe or suggest the use of cells transfected with ion channel coding sequences for the purpose of modifying the function of excitable tissues.

It should be noted in this respect, that subsequent articles published by Donhaue et al. as well as subsequent patent applications to Donahue et al. are all focused at gene therapy for the treatment of cardiac disorders [see e.g., a late review by Donahue et al. (2005) Ann. N. Y. Acad. Sci. 1047:157-165 as well as Donahue et al. Trends Cardiovasc. Med. 2005 15:219-24; Donahue et al. Ann. Med. 2004 36:98-105; Donahue et al. Nat. Med. 2000 6:1395-8; abstracts of which are attached herewith]. This is even more surprising given that the art of Koh et al. has been known for years.

All this points to the fact that the teachings of Donahue et al. and/or Koh et al. could not motivate the skilled artisan of using heterologous ion channel expressing cells for the treatment of cardiac disorders.

Notwithstanding the above arguments, Applicant wishes to point out that since both Donahue et al. and Koh et al. failed to describe, suggest or mention the treatment of disorders other than cardiac disorders, it is the Applicant's strong opinion that the Examiner mistakenly rejected claims 35, 42, 48 and 54, which scope is regulation of neuronal discharge. Accordingly claims 32 and 51 have now been amended to to encompass excitable tissues other than the heart (e.g., pancreas, kidney, brain or liver) and should be deemed allowable.

Additionally, Applicant wishes to point out that both Donahue et al. and Koh et al. failed to describe, suggest or mention modification of cells other than cardiomyocytes. Accordingly new claims 68-83, which pertain to the use of cells other than cardiomyocytes have now been added and should be deemed allowable. Support for this claim language can be found throughout the instant application. See e.g., Page 11 - Last Paragraph.

Yet additionally, Applicant wishes to point out that both Donahue et al. and Koh et al. failed to describe, suggest or mention treating cardiac disorders other than the elimination of arrhythmogenic focus or the correction of intra cardiac conduction defect using ion channels. Accordingly new claims 64-67, have now been added and should be deemed allowable. Support for this claim language can be found throughout the instant application such as in Page 37 line 16 and Page 38 - Last Paragraph.

While strongly traversing the above combination of references proposed by the Examiner, Applicant, in order to simplify the issues, attaches herewith a Declaration under 37 C.F.R. §1.131 by Applicant Yair Feld in which he shows a reduction to practice of the claimed invention prior to the effective filing date of the Donahue et al. publication, which is the September 6, 2000 filing date of the priority Provisional Patent Application 60/230,311 of

Donahue et al. A supporting Declaration of Gal Ehrlich, a licensed Israeli patent attorney, is also attached, corroborating said making of the invention prior to September 6, 2000.

In view thereof, the reference to Donahue et al. is not prior art reference relative to the instant application, and the sole rejection of the claims over Donahue et al. in view of Koh et al. (1995) is no longer valid and should be withdrawn.

In view of the foregoing, it is respectfully submitted that this application is in condition for allowance. An early Notice of Allowance of claims 23, 24, 28-33, 35, 40, 42-46, 48-52 and 54-56, 59-60 and 61-83 is earnestly solicited.

Respectfully submitted,

Martin Moynihan
Registration No. 40,338

Date: October 23, 2005

Enclosures:

1. Additional Claim Fee
2. Declaration Under 37 C.F.R. §1.131
3. Supporting Declaration Under 37 C.F.R. §1.131
4. Exhibits A-D
5. J. k. DONAHUE et al., "Modification of Cellular Communication by Gene Transfer", (2005) Ann. N. Y. Acad. Sci. 1047:157-165
6. J. K. DONAHUE et al., "Gene Therapy for Cardiac Arrhythmias", Trends Cardiovasc. Med., 2005, 15(6):219-24 (first page)
7. J. K. DONAHUE et al., "Gene Transfer Techniques for Cardiac Arrhythmias", Ann. Med., 2004, 36 Suppl 1:98-105 (first page)
8. J. K. DONAHUE et al., "Focal Modification of Electrical Conduction In The Heart By Viral Gene Transfer", Nat. Med. 2000 December, 6(12):1395-8 (first page)
9. G. F. TOMASELLI et al., "Somatic Gene Transfer and Cardiac Arrhythmias: Problems and Prospects", Journal of Cardiovascular Electrophysiology, Vol. 14 No. 5, May 2003